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FISH & RICHARDSON PC
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MINNEAPOLIS, MN 55440-1022

EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/763,049	ROBINSON ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7,11-14,20-22,32-35,38,42,43,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7,11-14,20-22,32-35,38,42,43,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 30 March 2009.

Claim Status

Claims 1, 7, 20, 38 and 38 are amended. Claims 4-6, 8-10, 15-19, 23-31, 36-37, 39-41, and 44-56 are canceled. Claims 57-58 are newly added. Claims 1-3, 7, 11-14, 20-22, 32-35, 38, 42-43, and 57-58 are under current examination.

Priority

This application claims benefit from as a CON of 08/187,879 filed on 01/27/1994 (US-PAT 6,841,381), which is a CIP of 08/009,833 filed on 01/27/1993 (US-PAT 5,643,578), which is a CIP of 07/855,562 filed 03/23/1992 (ABN). The instant application has been granted the benefit date, 23 March 1992, from the application 07/855,562.

The applicant has indicated that the following limitations have been removed from the pending claims: (1) SIV antigen, (2) rotavirus antigen, (3) microsphere encapsulation of DNA, (4) methods of immunization comprising combinations of influenza antigens. The examiner had asserted that parent priority document, US-PAT 5,643,578, does not have benefit of these limitations and would there.

The instant application has been granted the benefit date, 23 March 1992, from the application 07/855,562.

RESPONSE TO ARGUMENTS

Double Patenting

The rejection of claims 1-3, 8, 11-23, 27, 30-35, 39, 42-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 of U.S. Patent No. 6,165,993 is withdrawn in response to the applicant's claim amendments and arguments. The applicant has removed all limitations directed to rotavirus epitopes from the pending claims. Therefore, the pending claims are not obvious over the claims of U.S. Patent No. 6,165,993. Accordingly, the examiner hereby withdraws the rejection of claims 1-3, 8, 11-23, 27, 30-35, 39, 42-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 of U.S. Patent No. 6,165,993

The rejection of claims 1-3, 8, 11-23, 27, 30-35, 39, 42-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 of U.S. Patent No. 6,187,319 is withdrawn in response to the applicant's claim amendments and arguments. The applicant has removed all limitations directed to rotavirus epitopes from the pending claims. Therefore, the pending claims are not obvious over the claims of U.S. Patent No. 6,165,993. Accordingly, the examiner hereby withdraws the rejection of claims 1-3, 8, 11-23, 27, 30-35, 39, 42-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 of U.S. Patent No. 6,187,319.

The rejection of claims 1-3, 6-7, 11-13, 16, 30-34, 37-38, 42-43, and 52-56 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 of U.S. Patent No. 5,643,578 (as first rejected in the Action, filed 9/25/2006 and maintained 5/4/2007) is withdrawn in response to the terminal disclaimer filed September 14, 2007. Accordingly, the examiner hereby withdraws the rejection of claims 1-3, 6-7, 11-13, 16, 30-34, 37-38, 42-43, and 52-56 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1-16 of U.S. Patent No. 5,643,578.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7, 11-14, 20-22, 32-35, 38, and 42-43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al. (WO90/11092) in view of Huylebroeck et al. (Gene. June 1988. 66(2): 163-81) and further in view of Townsend et al. (Cell. November 1984; 39(1):13-25) and further in view of Atkinson et al. (US-4,861,864, issued 29 Aug 1989) and further in view of Andrianov et al. (US-5,529,777, issued 25 June 1996) for the reasons of record and the comments below. *In addition, the pending rejection is extended to include newly added claims 57-58.*

Applicant's arguments (Remarks, pages 6-12) and claim amendments, filed 30 March 2009 regarding rejection of claims 1-3, 7, 11-14, 20-22, 32-35, 38, and 42-43 under 35 USC 103 have been fully considered but they are unpersuasive.

The applicant has amended the pending claims by cancelling all limitations directed to rotavirus epitopes and by adding the claim limitations, immunization "prior to infection by an influenza virus." The new claims 57-58 contain limitations directed to "CMV promoter."

The applicant has made several arguments.

The most important argument in traversal of the pending 35 USC 103 rejection is that the cited art (specifically, Felgner) does not provide evidence of "protective immunity" from the nucleic acid vaccinations (Remarks, page 9, lines 9-11). The specification does not provide an explicit definition of the phrases, "protective immunity" or "protective immune response." Claim 1 indicates "a protective immune response compris[es] a humoral immune response, a cell-mediated immune response, or both is elicited against the antigen." The instant specification indicates that a humoral immune response induces antibodies against viral envelope proteins (page 12, lines 1-5). Felgner also teaches that humoral immunity involves antibodies secreted into the body fluids and which directly recognize an antigen (page 2, lines 9-11). Example 8 of Felgner et al. teach a mRNA vaccination of mice with gp120 protein of HIV virus (pages 55-56) and subsequent analysis of antibodies produced in the mouse with are immunogenic against gp120. In an art recognized *in vitro* assay system having CD4+ cells, Felgner et al demonstrated that mouse serum containing anti-gp120 antibodies from the vaccinated mice is able to lyse the CD4+ cells (page 56). Felgner et al. conclude the "protective effect of gp120 immune serum is determined as the reduction in the number of plaques in the batches of cells treated with both gp120 mRNA vaccinated mouse serum and HIV compared to the number of batches treated with HIV alone" (page 56, lines 18-23, emphasis added by examiner). In this experiment, Felgner demonstrates a humoral immunity protective effect against the HIV infection of cells. While Felgner et al. does not show "clearance" of the virus from a whole

vertebrate system in a shorter time than mock-vaccinated animals, as the inventor does in his examples, Felgner does, indeed, demonstrate that the mice have developed indicators of a protective humoral immune response, namely the serum of the mice (containing anti-HIV antibodies) is able to reduce the number of CD4+ cells killed by HIV. This humoral response is protective against subsequent infection by the virus. The examiner does not believe that Felgner does not need to exactly replicate the inventor's examples to suggest the limitations of the instant claims. The Felgner reference clearly suggests the ability to induce a humoral immune response against a viral epitope using nucleic acid vaccines. Further, the Felgner reference also demonstrates that the antibodies and other factors induced by the nucleic acid vaccine have the ability to protect cells against subsequent exposure to virus. As the scope of the claims provides only general parameters for providing a "protective immune response" and Felgner does teach or suggest a "protective immune response," the examiner finds the applicant's argument unpersuasive.

The applicant has also suggested that the instant invention is not obvious over the cited art because the cited art is not predictable in producing protective immune response in a subject from a subsequent viral infection (Remarks, page 8, lines 4-11). According to the instant claims, specification and cited art, a protective immune response comprises a humoral immune response, a cell-mediated immune response, or both is elicited against the antigen. As discussed above, in Example 8, Felgner et al. demonstrated that a humoral response (i.e., antibodies and other factors) is produced by administration of nucleic acids encoding viral antigens. Implicit in Felgner's

teachings is that the viral epitopes were produced within the animal's cells after nucleic acid administration. Felgner theorizes that cell-mediated immune responses would be elicited if cell surface-antigens (e.g., viral coat proteins) were expressed by mRNA (page 40, lines 9-14). In addition, Example 9 of Felgner shows in a nude mouse with a reconstituted human immune system, nucleic acid vaccination of these mice showed an anti-viral protection after subsequent infection of the mouse with a virus (page 57, lines 24-25). To the examiner, the Felgner reference seems to indicate that there is some predictability in producing protective immune response in a subject from a subsequent viral infection. Therefore, the examiner finds the applicant's arguments unpersuasive.

The applicant has noted that due to the claim amendments, Adkinson and Andrianov references are no longer necessary for the rejection. These references were introduced to account for limitations directed to rotavirus antigens and alginate polymers. While currently unnecessary, these references will not be removed in the present action.

Accordingly, the examiner hereby maintains the rejection of claims 1-3, 7, 11-14, 20-22, 32-35, 38, and 42-43 under 35 U.S.C. 103(a) as being unpatentable over Felgner et al. in view of Huylebroeck et al. and further in view of Townsend et al. and further in view of Atkinson et al. and further in view of Andrianov et al.

In addition, newly added claims 57-58 are directed to the methods of claim 1 and 32 respectively, wherein the promoter of the plasmid vectors comprises a cytomegalovirus promoter. Felgner et al. teach plasmid constructs having a viral coat protein gene operably linked to a cytomegalovirus (CMV) promoter (page 70, Example

19). Therefore, the pending rejection is extended to encompass the rejection of claims 57-58.

The examiner reiterates the rejection of from the previous Action, below:

Claims 1-3, 7, 11-14, 20-22, 32-35, 38, 42-43 and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al. (WO90/11092) in view of Huylebroeck et al. (Gene. June 1988. 66(2): 163-81) and further in view of Townsend et al. (Cell. November 1984; 39(1):13-25) and further in view of Atkinson et al. (US-4,861,864, issued 29 Aug 1989) and further in view of Andrianov et al. (US-5,529,777, issued 25 June 1996).

Claims 1 and 16-17 are directed to methods of immunizing a vertebrate using a composition consisting essentially of a set of plasmid vectors in a physiologically acceptable medium, the plasmid vectors comprising DNA encoding an influenza virus antigen or a rotavirus antigen operatively linked to a DNA promoter, which elicits a humoral and/or cell-mediated immune response against a desired antigen. Claim 4 is directed to the limitation that the method is capable of eliciting a protective immune response. Claims 7 and 25-26 are directed to the further limitation that the virus is an influenza virus and the antigen is hemagglutinin. Claims 8 and 27 are directed to the further limitation that the virus is a rotavirus. Claims 30-31 are directed to the limitations of delivery to a "human mammal." Claim 32 is directed to using a gene gun to administer the compositions of the invention. Claims 15 and 23 are directed to administration of microsphere encapsulated plasmid vectors in a physiologically acceptable medium. The instant specification does not specifically define the scope of

"microsphere encapsulated plasmid vectors." The specification's sole embodiment of microsphere encapsulated plasmid vectors is as alginate microspheres. Furthermore, the specification does not exclude liposome microspheres from being considered pharmaceutically acceptable.

Felgner et al. teach plasmid vectors comprising "therapeutic polynucleotides... [which] code for immunity-conferring polypeptides, which act as endogenous immunogens to provoke a humoral or cellular response, or both" (page 17, lines 31-34). Felgner et al. suggest that tumor-specific antigens and viral protein antigens are appropriate for use in their invention (for example, page 4). Felgner et al. also teach intradermal, intramuscular administration (page 11, lines 33-37) of naked polynucleotides in pharmaceutically acceptable carriers (page 8, line 24) to vaccinate a human (page 8, line 34). Furthermore, Felgner et al. teach "polynucleotides may be...delivered into muscle or skin using a vaccine gun" (page 36, lines 15-18). Felgner et al. also teach liposomal microsphere formulations of plasmid DNA and administration to the lung; the examiner believes this satisfies the limitations directed to pharmaceutically acceptable microsphere encapsulated plasmid vectors, in light of the teachings of the specification, described above. Claims 57-58 are directed to the methods of claim 1 and 32 respectively, wherein the promoter of the plasmid vectors comprises a cytomegalovirus promoter. Felgner et al. teach plasmid constructs having a viral coat protein gene operably linked to a cytomegalovirus (CMV) promoter (page 70, Example 19).

Felgner et al. do not teach specific antigens for influenza or rotavirus. Felgner et al. also do not specifically teach administration of set of plasmids encoding antigens, although they do teach co-transfection of two different plasmids to the cells.

Huylebroeck et al. teach plasmid DNA mediated gene transfer of two different influenza A antigens, including H1 hemagglutinin (abstract). Huylebroeck et al. teach cotransfection of plasmids and co-expression of hemagglutinin A and influenza matrix protein M_1 in animal cells.

Townsend et al. teach plasmids comprising hemagglutinin antigens. Townsend et al. also teach "isolated full-length influenza gene clones is now routine" (page 13, col.2). Furthermore, Townsend et al. teach, "there are implications for vaccine design…a vaccine that presents nucleoprotein in an appropriate form that could stimulate crossreacrtive CTL memory might be crossprotective between pandemic influenza A viruses" (page 22, col.2).

Atkinson et al. teach a plasmid comprising cDNA of a rotavirus antigen for expression of VP7 (col. 4, lines 39-42). Atkinson et al. teach that an object of their invention is to provide a neutralizing antigen to rotavirus which is readily disseminated throughout the body with the concomitant greater exposure to the immune system (col.2, lines 34-37).

Huylebroeck et al. and Townsend et al. and Atkinson et al. do not specifically teach DNA vaccines. These references also do not teach immunization using sets of plasmids encoding the antigens.

Andrianov et al. teach "polymeric hydrogels are used to encapsulate antigen to form vaccines....microparticles are formed ....preferred polymers are alginate" (abstract) and "enhanced immunogenicity of microspheres formed of 95% alginate" (col., lines) and methods of oral and mucosal delivery. Andrianov et al. teach "the polymer is used to deliver nucleic acid which encodes antigen to cells where the nucleic acid is expressed" (col.12, lines 39-42).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to immunize a vertebrate against an influenza virus or rotavirus by administering a composition consisting essentially of a set of plasmid vectors comprising DNA encoding either influenza virus antigens or rotavirus antigens. Furthermore, it would have been obvious to use microencapsulation of plasmid DNA or gene gun to administer the DNA vaccines. In addition, it would have been obvious to use sets of plasmids to administer plasmids comprising antigens.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Each of the elements (plasmids comprising influenza or rotavirus antigens, methods of DNA vaccination, and gene gun administration) are taught by Felgner et al. or Huylebroeck et al. or Townsend et al. or Atkinson et al. and further they are used as vaccines or are shown to be involved in inducing Cytotoxic T Lymphocyte responses. It

would be therefore predictably obvious to use a combination of these elements in a DNA vaccine. The methods of combining the elements with "sets of plasmids" are predictable; and therefore they are likewise obvious. Co-administration of plasmids has been performed in the art and is merely a variation of administration. Also, Andrianov et al. suggests alginate microspheres for use in vaccines; therefore, it would be obvious to apply this technology to plasmid DNA vaccine formulations.

Therefore the method as taught by Felgner et al. in view of Huylebroeck et al. and further in view of Townsend et al. and further in view of Atkinson et al. and further in view of Andrianov et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SDL/ Scott Long
Patent Examiner, Art Unit 1633

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633